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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/887,496 | 06/22/2001 | Partha S. Banerjee | 18025-1014 | 7707 |

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| EXAMINER |
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BAHAR, MOJDEH

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| ART UNIT | PAPER NUMBER |
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1617

DATE MAILED: 05/20/2003

19

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/887,496

Applicant(s)

BANERJEE ET AL.

Examiner

Mojdeh Bahar

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 February 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-64, 69-83, 87-89, 93 and 99-121 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-64, 69-83, 87-89, 93 and 99-121 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>16 & 18</u> . | 6) <input type="checkbox"/> Other: |

DETAILED ACTION

Applicant's response to the office action of December 18, 2002 submitted March 4, 2003 is acknowledged.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-64, 69-83, 87-89, 99-112 and 117-119 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hochrainer et al. (6,150,418) in view of Bartow et al. and PDR.

Hochrainer et al. (6,150,418) teaches a pharmaceutical composition comprising formoterol suitable for storage, in the form of a solution or suspension for use in inhalers, see abstract in particular. Hochrainer et al. (6,150,418) further teaches that the pharmaceutical composition is such that it can be administered by inhalation using a suitable nebuliser, see col. 4, lines 19-20 and col. 5, lines 33-41. Hochrainer et al. (6,150,418) further teaches that the pH range (preferably between 2.0-7.0 and most preferably between 4.5-5.5), the employment of

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inorganic acids such as phosphoric acids and the employment of buffers in its composition, see in particular col.3, lines 35-40 and col.4, line 55 to col. 5, line 7. Hochrainer et al. (6,150,418) teaches the concentration of formoterol to be between about 75 mg/ml and about 500 mg/ml, see in particular claims 1-4. It also teaches that the suspending agent is a protic liquid, a mixture of water and sodium chloride. Hochrainer et al. (6,150,418) finally teaches that additional active ingredients such as steroids could be incorporated in its composition, see claim 19.

Hochrainer et al. (6,150,418) does not particularly teach the employment of fluticasone propionate or its concentration in its pharmaceutical composition. Neither does it teach a kit.

Bartow et al. teaches that Formoterol, a selective beta 2 adrenoceptor agonist is an effective bronchodilator. Bartow further teaches that the addition of inhaled formoterol to corticosteroid (e.g., budesonide) regimens improves lung function and reduces asthma symptoms, see pages 304 and 305.

PDR teaches fluticasone propionate as a known corticosteroid readily employed in methods of treating asthma, see flovent.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ fluticasone propionate in the composition of Hochrainer et al. (6,150,418) employed in a method of treating asthma. It would have also been obvious to include the pharmaceutical composition in a kit.

One of ordinary skill in the art would have been motivated to employ fluticasone propionate in the composition of Hochrainer et al. because both fluticasone propionate and formoterol are known to be useful in treating asthma. Combining two agents which are known to be useful to treat asthma individually into a single composition useful for the very same

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purpose is prima facie obvious. See *In re Kerkhoven* 205 USPQ 1069. Optimization of amounts and inclusion of a pharmaceutical composition in a kit are also within the purview of the Skilled Artisan and is therefore obvious.

Claim 93 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hochrainer et al. (6,150,418) in view of Bartow et al. and PDR as applied to claims 1-64, 69-83, 87-89, 99-112 and 117-119 above, and further in view of PDR.

Hochrainer et al. (6,150,418) in view of Bartow et al. and PDR taken together do not teach the employment of a third active in their composition.

PDR at pages 48-482, 535,537, and 2828-9 teaches that albuterol (beta2 adrenoreceptor agonist), accolate (leukotriene receptor antagonist) and Zyflo (5-lipoxygenase inhibitor) are all known to be effective in treating asthma.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ a third active such as those enumerated immediately above in a combination composition along with formoterol and fluticasone.

One of ordinary skill in the art would have been motivated to employ a third active such as those enumerated immediately above in a combination composition along with formoterol and fluticasone because all three actives are known to be useful in treating asthma. Combining two agents which are known to be useful to treat asthma individually into a single composition useful for the very same purpose is prima facie obvious. See *In re Kerkhoven* 205 USPQ 1069. Optimization of amounts and inclusion of a pharmaceutical composition in a kit are also within the purview of the Skilled Artisan and is therefore obvious.

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Claims 113-116 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hochrainer et al. (6,150,418) in view of Bartow et al. and PDR as applied to claims 1-64, 69-83, 87-89, 99-112 and 117-119 above, and further in view of Hardman et al. (*Goodman Gilman's The Pharmacological Basis of Therapeutics*, 1996, page 665).

Hochrainer et al. (6,150,418) in view of Bartow et al. and PDR taken together do not teach the employment of ipratropium bromide in their composition, nor do they teach the exact weight percentage of ipratropium bromide in their composition.

Hardman et al. teaches that ipratropium bromide is an anticholinergic agent useful in treating asthma.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ ipratropium bromide in a combination composition along with formoterol and fluticasone.

One of ordinary skill in the art would have been motivated to employ ipratropium bromide in a combination composition along with formoterol and fluticasone because all three actives are known to be useful in treating asthma. Combining two agents which are known to be useful to treat asthma individually into a single composition useful for the very same purpose is prima facie obvious. See *In re Kerkhoven* 205 USPQ 1069. Optimization of amounts is within the purview of the Skilled Artisan and is therefore obvious.

Claims 113-116 (in so far as they read on tiotropium bromide) and 120-121 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hochrainer et al. (6,150,418) in view of Bartow et al. and PDR as applied to claims 1-64, 69-83, 87-89, 99-112 and 117-119 above, and further in view of Leckie et al (*Novel Therapy of COPD, abstract, Jan 2000*)..

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Hochrainer et al. (6,150,418) in view of Bartow et al. and PDR taken together do not teach the employment of tiotropium bromide in their composition, nor do they teach the exact weight percentage of tiotropium bromide in their composition.

Leckie et al teaches that tiotropium is a known bronchodilator employed in treatment of asthma.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ tiotropium bromide in a combination composition along with formoterol and fluticasone.

One of ordinary skill in the art would have been motivated to employ tiotropium bromide in a combination composition along with formoterol and fluticasone because all three actives are known to be useful in treating asthma. Combining two agents which are known to be useful to treat asthma individually into a single composition useful for the very same purpose is prima facie obvious. See *In re Kerkhoven* 205 USPQ 1069. Optimization of amounts is within the purview of the Skilled Artisan and is therefore obvious.

Response to Arguments

Applicant's arguments filed February 14, 2003 have been fully considered but they are not persuasive. Applicant traverses the rejection based on the primary reference, Hochrainer et al. stating the same arguments as presented in response to the first office action. For the reasons of record (Non Final Action of 12/18/2002) this rejection is maintained. Applicant argues that Hochrainer teaches two separate compositions, one stable concentrate and one composition suitable for direct administration. Note that nowhere does Hochrainer teach that its composition

suitable for direct administration is unstable. Applicant quotes a section of Hochrainer on page 7 of the response, where Hochrainer states:

“In the past it has been found that liquid aerosol formulations of formoterol are not suitable for use in inhalers[...] formoterol cannot be stored in a sufficiently stable manner in solution to guarantee the pharmaceutical quality of the formulation over lengthy periods of time.”

Note that this quotation merely reports what was known in the art prior to the Hochrainer patent and cannot be construed to mean that the Hochrainer pharmaceutical composition itself will be unstable. Also note that a formulation claimed by Hochrainer fits within the ranges claimed in the instant application, see claim 22. The concentration of formoterol in this formulation is about 0.9 to 1.5 mg/ml which overlaps with the formoterol concentration claimed herein, see for example claims 22 and 39 of the instant application.

Note that applicant has structured all his arguments based on the his first argument, i.e., that the secondary references do not cure the defects of Hochrainer et al. since they do not teach composition stability and that the composition is suitable for direct administration. For the reasons of record and those discussed herein immediately above the obviousness rejection is maintained.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mojdeh Bahar whose telephone number is (703) 305-1007. The examiner can normally be reached on (703) 305-1007 from 8:30 a.m. to 6:30 p.m. Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, can be reached on (703) 305-1877. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Mojdeh Bahar
Patent Examiner
May 16, 2003


SREENI PADMANABHAN
PRIMARY EXAMINER

5/19/03